

Evaluating the potential of JCV DNA in CSF as an endpoint in clinical trials for PML product development

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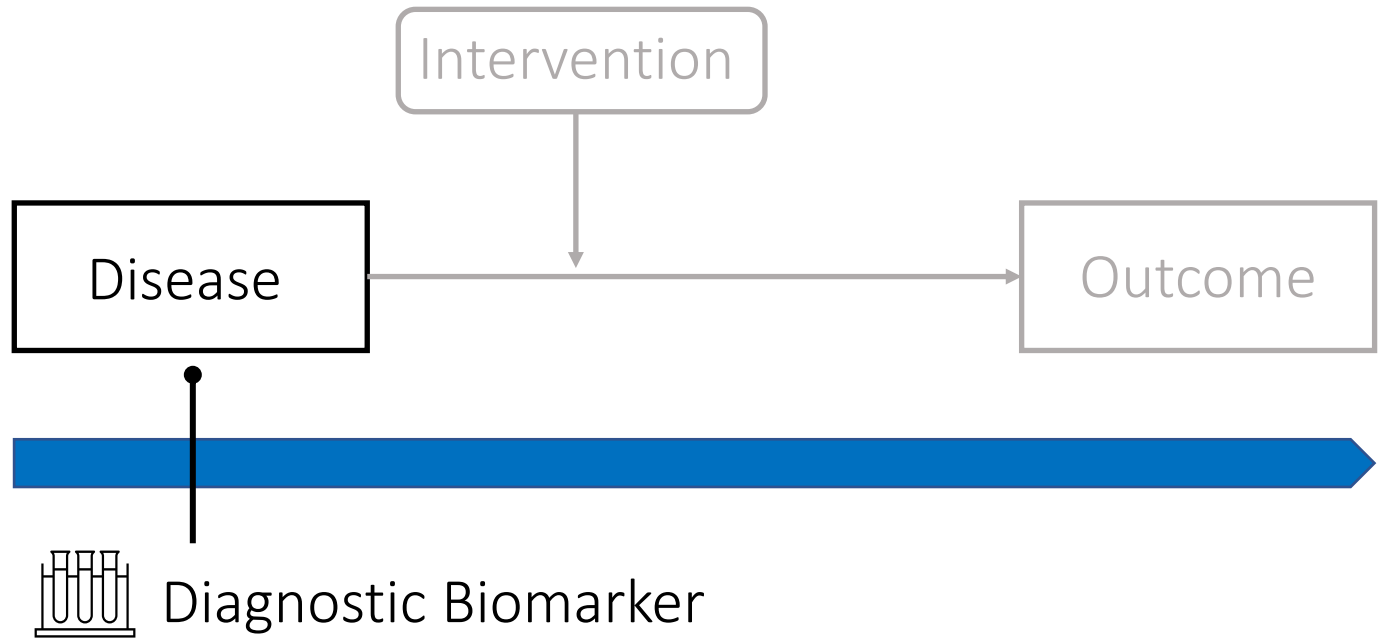
Eugene Major, PhD

Guillaume Martin-Blondel, MD, PhD

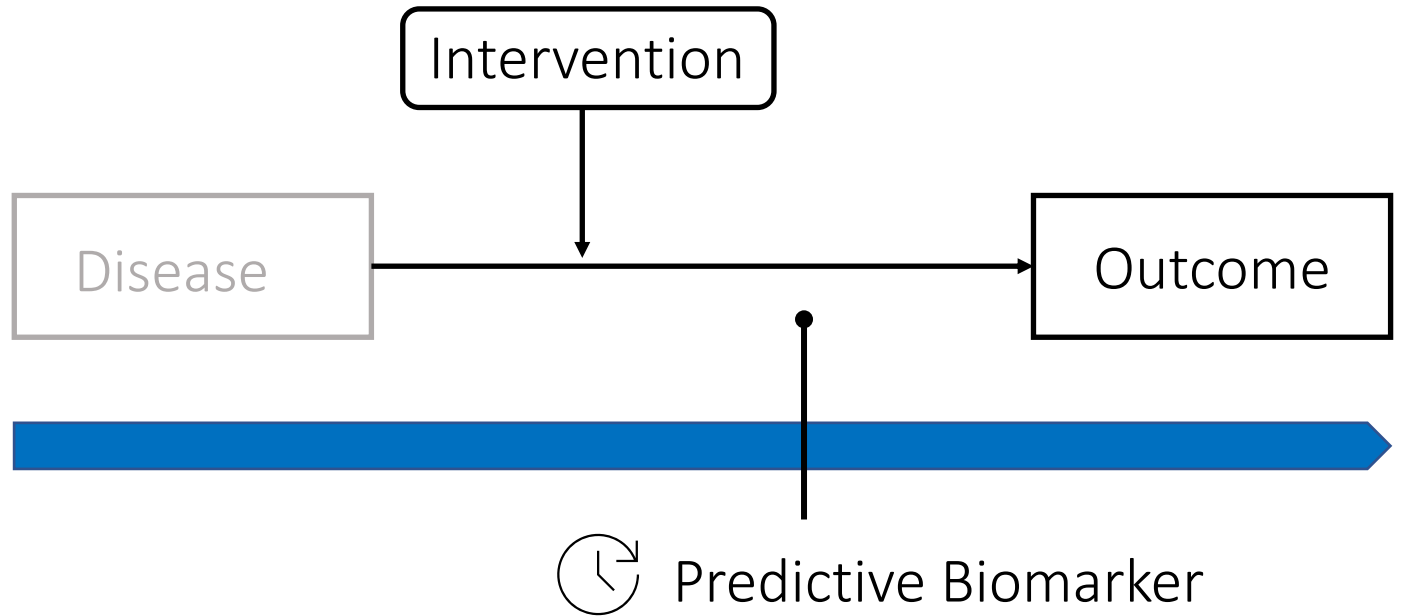
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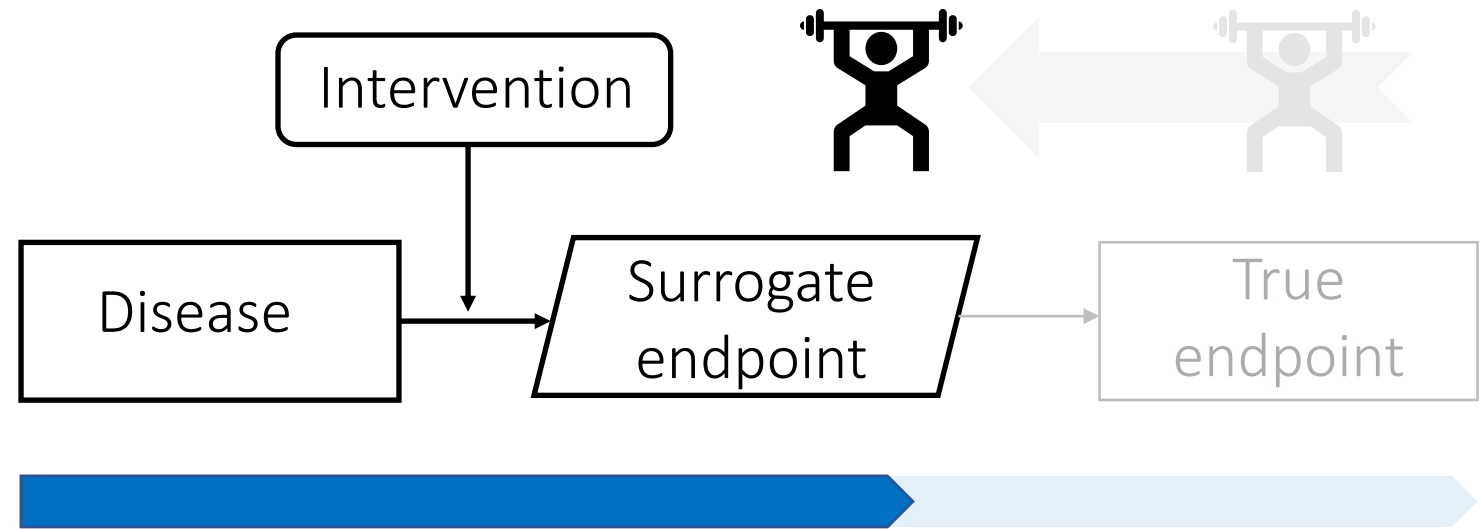
Current use of CSF JCV PCR



Is CSF JCV
DNA suitable
as a clinical
trial efficacy
endpoint?



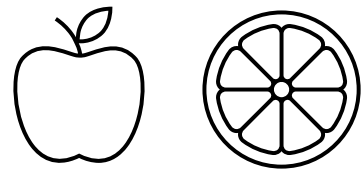
Is CSF JCV
DNA suitable
as a surrogate
endpoint?



Sources of technical variability

(over time, across labs)

- Methodology
- Assay sensitivity
- Assay standards



True meta-analysis not possible

Methods

1

PubMed Literature Search

*PCR AND JCV AND
progressive multifocal
leukoencephalopathy*

Methods

1

PubMed Literature Search

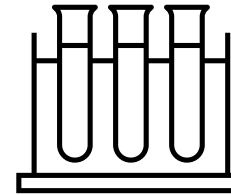
*PCR AND JCV AND
progressive multifocal
leukoencephalopathy*

2

LMMN CLIA Database

452 unique patients

942 samples



Methods

1

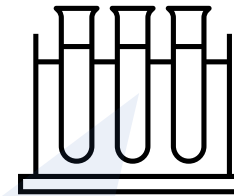
PubMed Literature Search

*PCR AND JCV AND
progressive multifocal
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2

LMMN CLIA Database

452 unique patients
942 samples

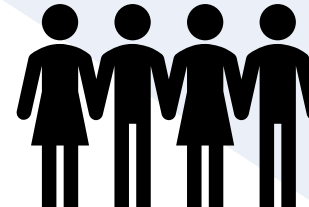


NIH PML cohort

48 patients

 21:18

mean age 57



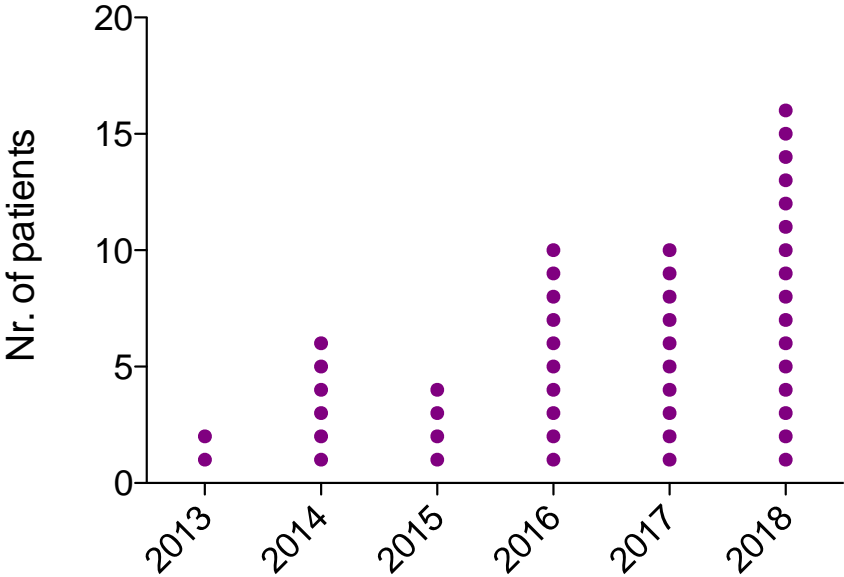
NIH PML cohort

PCR assay:
LMMN CLIA lab
LLD 10c/ml

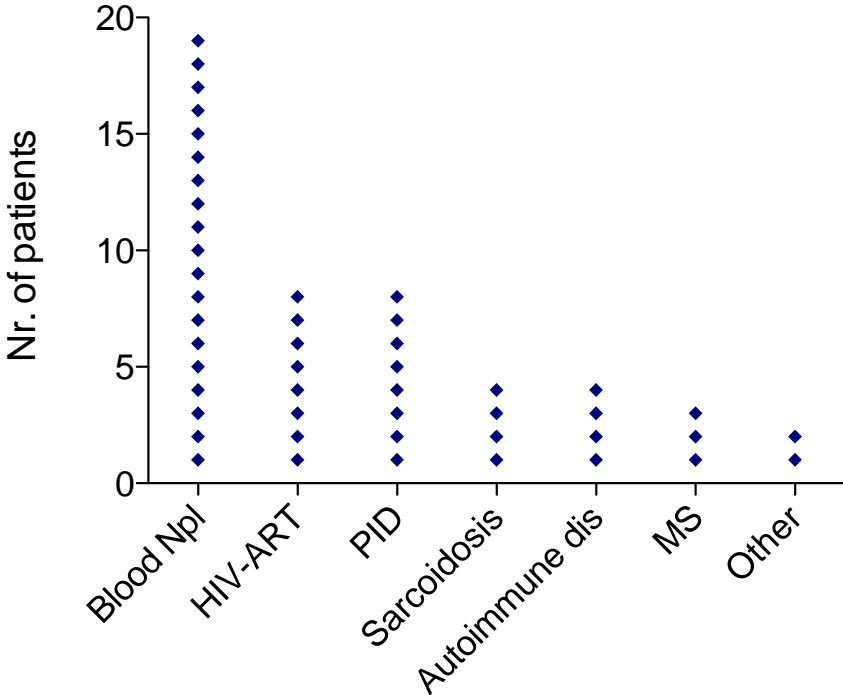
Total: 48 patients

- With FU sample at 30 days: 16
- With FU sample at 60 days: 23

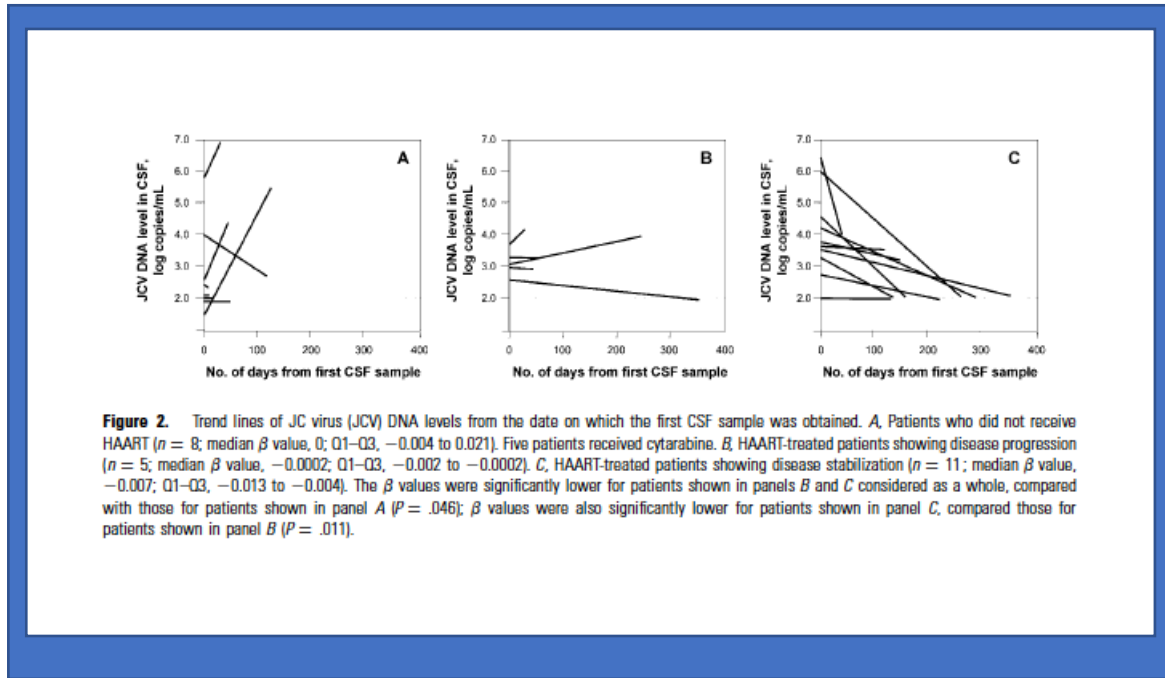
Case distribution by calendar year



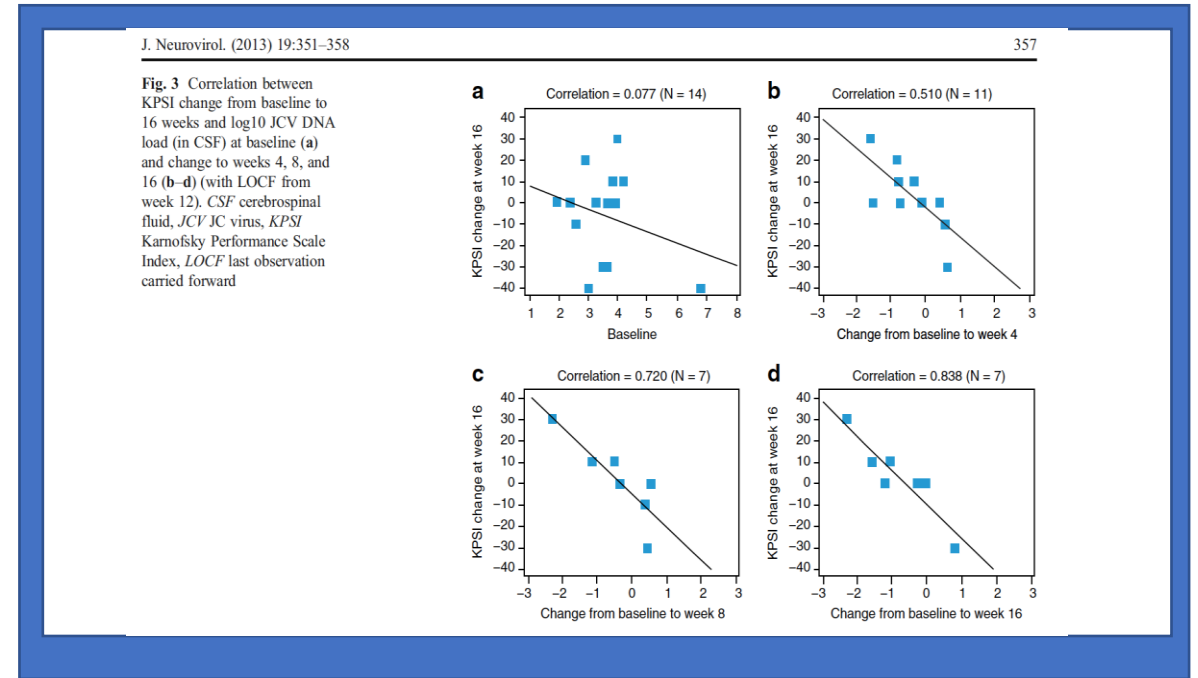
Case distribution by underlying disease



1 CSF JCV DNA as a trial endpoint



Bossolasco et al, 2005
n=61

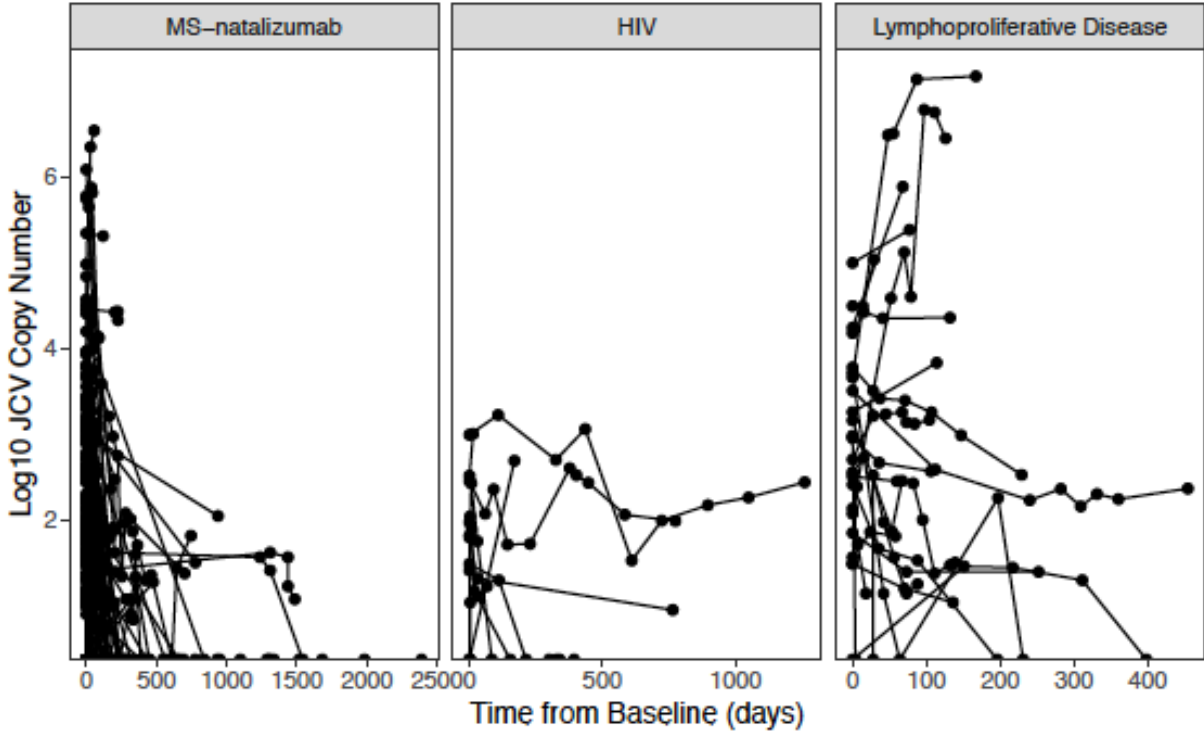


Clifford et al, 2013
n=14

- Declining CSF copy number seen in patients with clinical stabilization, but not in untreated patients or those with progression of PML
- Decline in CSF copy number associated with improved disability outcomes

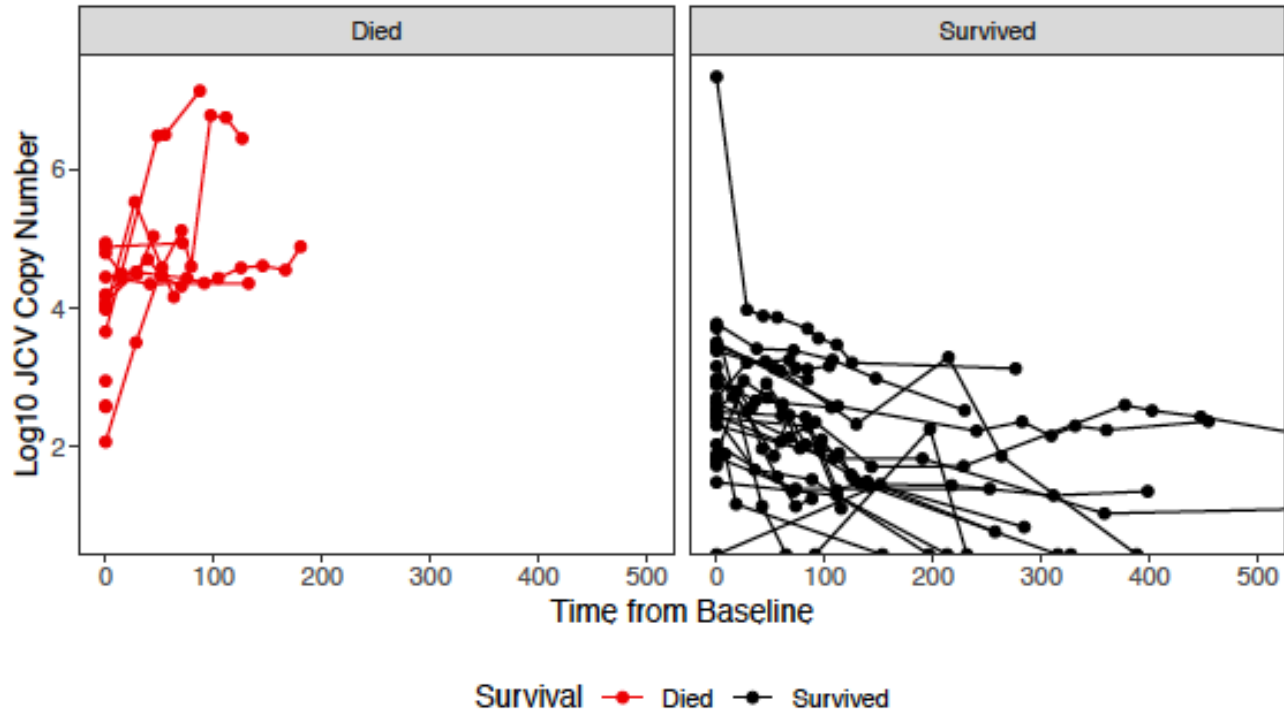
2

CSF JCV DNA as a trial endpoint



LMMN CLIA Database:
Longitudinal change in CSF JCV copy number across underlying disease

2 CSF JCV DNA as a trial endpoint



NIH PML Clinical Cohort:

- All those who died of PML had increase in CSF copy number over time
- 87.5% of those that survived PML had decrease or stabilization of CSF copy number over time

Methods

①

Three timepoints of interest were identified (30, 60, and 90 days), each with +/- 14 day window

②

Individuals were classified as having a decline in log₁₀ JCV DNA copy number (0.25, 0.5, or 1.0 log₁₀ decline)

③

Individuals were classified as surviving greater than 6 months, 9 months, or 12 months

Results

①

Survival at 6 months may not be of particular interest (6 month data calculated but not shown)

②

Survival was not different between 9 months and 12 months (9 month data calculated but not shown)

③

Futility measures were also considered but aren't shown here for brevity

Methods

	Survived > 6 months	Did not survive > 6 months
$\geq 0.25 \log_{10}$ decline		
$< 0.25 \log_{10}$ decline		

Methods

	Survived > 6 months	Did not survive > 6 months
$\geq 0.25 \log_{10}$ decline		
$< 0.25 \log_{10}$ decline		

	Survived > 6 months	Did not survive > 6 months
$\geq 0.50 \log_{10}$ decline		
$< 0.50 \log_{10}$ decline		

Methods

	Survived > 6 months	Did not survive > 6 months
$\geq 0.25 \log_{10}$ decline		
$< 0.25 \log_{10}$ decline		

	Survived > 6 months	Did not survive > 6 months
$\geq 0.50 \log_{10}$ decline		
$< 0.50 \log_{10}$ decline		

	Survived > 6 months	Did not survive > 6 months
$\geq 1.0 \log_{10}$ decline		
$< 1.0 \log_{10}$ decline		

NIH PML cohort

* Fisher's exact test

Time	Definitions	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 30	$\geq 0.25 \log_{10}$ decline	16	8/9 (89)	3/7 (43)	8/11 (73)	4/5 (80)	0.11
	$\geq 0.5 \log_{10}$ decline	16	4/4 (100)	7/12 (58)	4/11 (36)	5/5 (100)	0.24
	$\geq 1 \log_{10}$ decline	16	2/2 (100)	9/14 (64)	2/11 (18)	5/5 (100)	1.0
Day 60	$\geq 0.25 \log_{10}$ decline	23	12/12 (100)	5/11 (46)	12/17 (71)	6/6 (100)	0.005
	$\geq 0.5 \log_{10}$ decline	23	5/5 (100)	12/18 (67)	5/17 (29)	6/6 (100)	0.27
	$\geq 1 \log_{10}$ decline	23	4/4 (100)	13/19 (68)	4/17 (24)	6/6 (100)	0.53
Day 90	$\geq 0.25 \log_{10}$ decline	15	7/7 (100)	5/8 (63)	7/12 (58)	3/3 (100)	0.20
	$\geq 0.5 \log_{10}$ decline	15	6/6 (100)	6/9 (67)	6/12 (50)	3/3 (100)	0.23
	$\geq 1 \log_{10}$ decline	15	4/4 (100)	8/11 (73)	4/12 (33)	3/3 (100)	0.52
Baseline	$<3 \log_{10}$	48	22/27 (82)	10/21 (49)	22/32 (69)	11/16 (69)	0.03
	$<4 \log_{10}$	48	29/37 (78)	3/11 (27)	29/32 (91)	8/16 (50)	0.003

NIH PML cohort

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NIH PML cohort

* Fisher's exact test

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	$<4 \log_{10}$	48	29/37 (78)	3/11 (27)	29/32 (91)	8/16 (50)	0.003

Results

1

CSF JCV DNA behavior at 30 and 60 days may be the most predictive

2

CSF JCV DNA declines of 0.25 \log_{10} or 0.50 \log_{10} might be most predictive

CSF JCV DNA
Analyses of
Two Additional
Independent
Cohorts (i.e.,
“Validation
Cohorts”)

1

Milan Cohort

2

Multicenter anti-PD1/IL7 cohort
(MC)

1

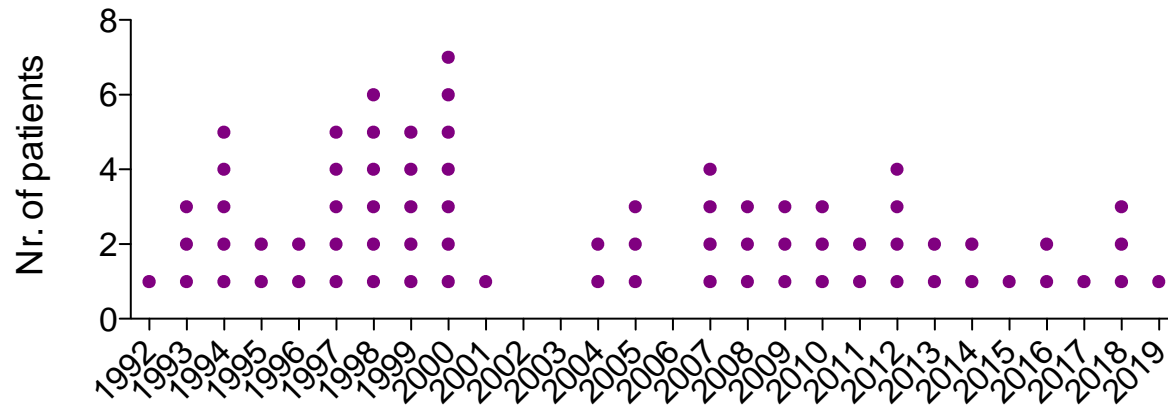
Milan cohort (*San Raffaele Hospital, Milan*)

Total: 73 patients

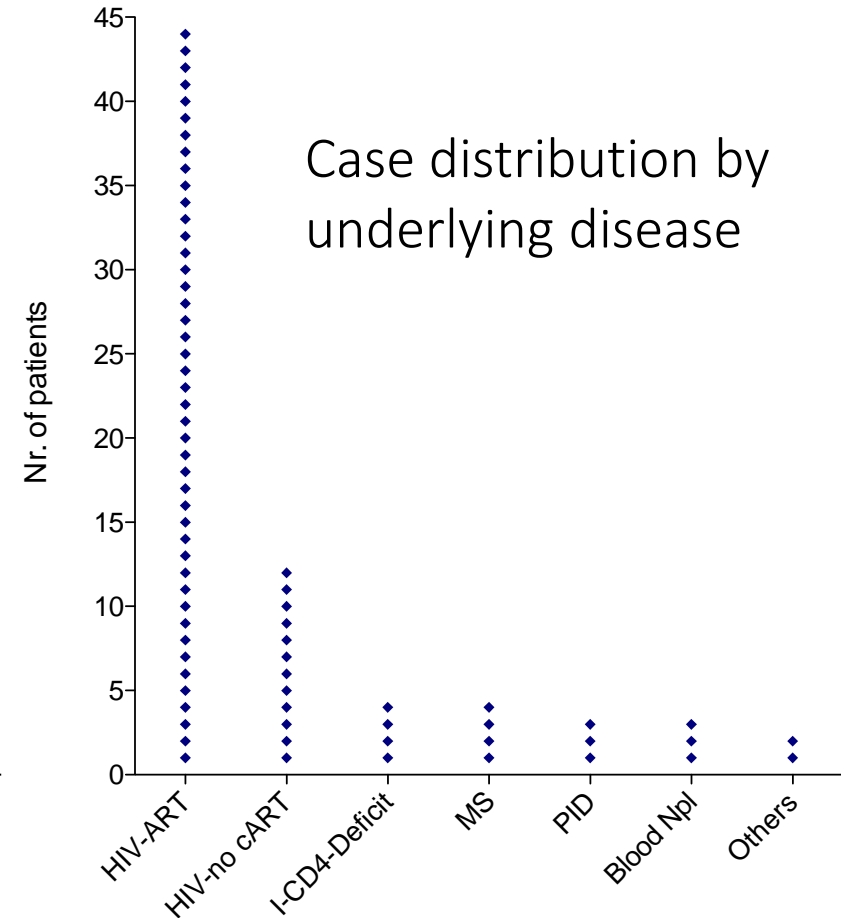
- With FU sample at 30 days: 46
- With FU sample at 60 days: 39

PCR assay:
In-house assay
LLD 100c/ml

Case distribution by calendar year



Case distribution by underlying disease



1 Milan cohort

Time	Definitions	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 30	$\geq 0.25 \log_{10}$ decline	46	7/12 (58)	7/34 (21)	7/18 (39)	23/28 (82)	0.17
	$\geq 0.5 \log_{10}$ decline	46	7/12 (58)	7/34 (21)	7/18 (39)	23/28 (82)	0.17
Day 60	$\geq 0.25 \log_{10}$ decline	39	8/13 (62)	8/27 (30)	8/15 (53)	20/24 (83)	0.03
	$\geq 0.5 \log_{10}$ decline	39	6/7 (86)	6/32 (19)	6/15 (40)	22/24 (92)	0.04
Baseline	$<3 \log_{10}$	73	15/33 (45)	15/40 (37)	15/30 (50)	18/43 (42)	0.17
	$<4 \log_{10}$	73	22/54 (41)	8/19 (42)	22/30 (73)	32/43 (74)	1.00

1 Milan cohort

Time	Definitions	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 30	$\geq 0.25 \log_{10}$ decline	46	7/12 (58)	7/34 (21)	7/18 (39)	23/28 (82)	0.17
	$\geq 0.5 \log_{10}$ decline	46	7/12 (58)	7/34 (21)	7/18 (39)	23/28 (82)	0.17
Day 60	$\geq 0.25 \log_{10}$ decline	39	8/13 (62)	8/27 (30)	8/15 (53)	20/24 (83)	0.03
	$\geq 0.5 \log_{10}$ decline	39	6/7 (86)	6/32 (19)	6/15 (40)	22/24 (92)	0.04
Baseline	$<3 \log_{10}$	73	15/33 (45)	15/40 (37)	15/30 (50)	18/43 (42)	0.17
	$<4 \log_{10}$	73	22/54 (41)	8/19 (42)	22/30 (73)	32/43 (74)	1.00

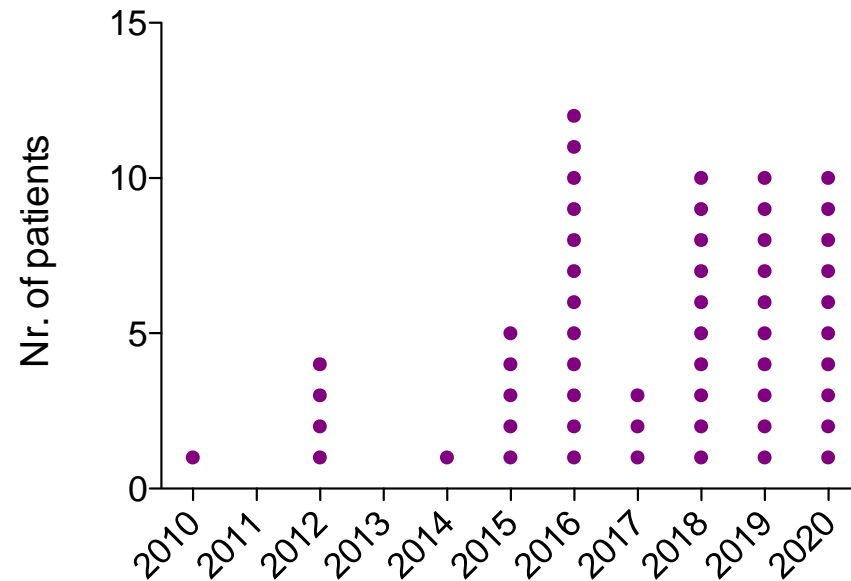
2 Multicenter anti-PD1/IL7 cohort (MC)

PCR assay:
multiple assays used

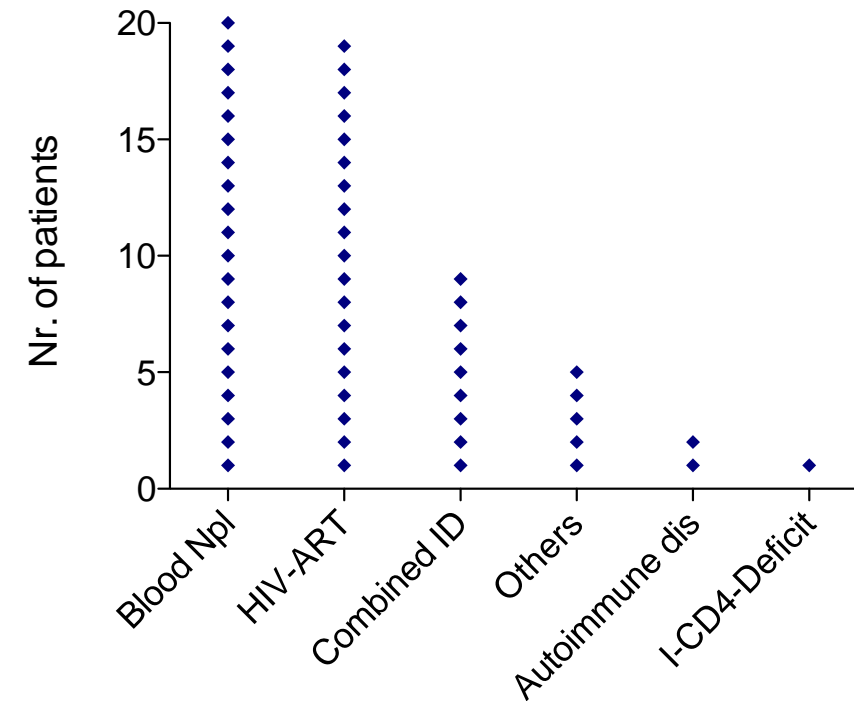
Total: 56 patients, from centers in Europe and the US

- With FU sample at 30 days: 21
- With FU sample at 60 days: 20
- Treated with rhIL: 34
- Treated with anti-PD1: 22

Case distribution by calendar year



Case distribution by underlying disease



2 Multicenter anti-PD1/IL7 cohort (MC)

Time	Definitions	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 30	$\geq 0.25 \log_{10}$ decline	21	6/9 (68)	3/12 (25)	6/9 (68)	9/12 (75)	0.09
	$\geq 0.5 \log_{10}$ decline	21	6/9 (68)	3/12 (25)	6/9 (68)	9/12 (75)	0.09
Day 60	$\geq 0.25 \log_{10}$ decline	20	9/10 (90)	4/10 (40)	9/13 (69)	6/7 (86)	0.06
	$\geq 0.5 \log_{10}$ decline	20	9/10 (90)	4/10 (40)	9/13 (69)	6/7 (86)	0.06
Baseline	$<3 \log_{10}$	56	11/21 (52)	19/25 (76)	11/30 (37)	16/26 (62)	1.0
	$<4 \log_{10}$	56	16/29 (55)	14/27 (52)	16/30 (53)	13/26 (50)	1.0

2 Multicenter anti-PD1/IL7 cohort (MC)

Time	Definitions	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 30	$\geq 0.25 \log_{10}$ decline	21	6/9 (68)	3/12 (25)	6/9 (68)	9/12 (75)	0.09
	$\geq 0.5 \log_{10}$ decline	21	6/9 (68)	3/12 (25)	6/9 (68)	9/12 (75)	0.09
Day 60	$\geq 0.25 \log_{10}$ decline	20	9/10 (90)	4/10 (40)	9/13 (69)	6/7 (86)	0.06
	$\geq 0.5 \log_{10}$ decline	20	9/10 (90)	4/10 (40)	9/13 (69)	6/7 (86)	0.06
Baseline	$<3 \log_{10}$	56	11/21 (52)	19/25 (76)	11/30 (37)	16/26 (62)	1.0
	$<4 \log_{10}$	56	16/29 (55)	14/27 (52)	16/30 (53)	13/26 (50)	1.0

Compiled key findings

Time	Definitions	Cohort	N	Survival among those meeting definition (PPV)	Survival among those <u>not</u> meeting definition (1-NPV)	Sensitivity	Specificity	P-value*
Day 60	≥ 0.25 log ₁₀ decline	NIH	23	100	46	71	100	0.005
		Milano	39	62	30	53	83	0.03
		MC	20	90	40	69	86	0.06
	≥ 0.5 log ₁₀ decline	NIH	23	100	67	29	100	0.27
		Milano	39	86	19	40	92	0.04
		MC	20	90	40	69	86	0.06

Conclusion

①

$\geq 0.25 \log_{10}$ CSF JCV DNA and $\geq 0.50 \log_{10}$ CSF JCV DNA declines at 60 days seem predictive of 12 month survival

②

Baseline CSF JCV DNA copy number is not strongly related to survival but may still be a key stratification variable

③

Validation cohorts provide support for these even with a varied patient background, treatment, and assays

Thank you

Special Acknowledgements

LMMN CLIA Laboratory, NIH

NIH Neuroimmunology Clinic

Infectious Diseases and Neurovirology Unit, San Raffaele Hospital, Milan

Contributing investigators from the Multicenter PD-1/IL7 Cohort